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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,731	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2008 and 02 January 2009*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *94-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *94-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/18/08 has been entered.

2. All previously pending claims have been cancelled. Claims 94-120 are under prosecution.

3. The IDS filed 1/2/09 has been considered. A signed copy of the 1449 is enclosed with this office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 94-117 and 120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. This is a rejection for new matter.

7. The claims all recite limitations wherein the expression is higher or lower "with a fold change of at least 2" or wherein the fold change is at least 2.5. The response does not identify basis for this aspect of the rejection. While the specification teaches that the ratio of expression of BTG2 between individuals having schizophrenia and healthy controls is 2.49the specification does not provide any basis for fold changes of 2, wherein two decimal places have been rounded away. All of the reports of fold expression change are carried out to two decimal places, suggesting that the extra places are valuable. There are many values between two and 2.49 which are lost by the dropping of these places. There is no evidence or teaching in the specification to suggest that values in this range would be indicative of schizophrenia.

8. Claims 94-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention is drawn to methods for indicating schizophrenia in a human test subject, methods for screening a human test subject for being a candidate for having schizophrenia, and methods for detecting expression of a BTG family, member 2 gene in a human test subject. The claims all include a step of quantifying the level RNA encoded by a BTG family, member2 (BTG2) gene in a blood sample obtained from said human and comparing the level with a quantified level of RNA encoded by said gene in blood samples from control subjects having schizophrenia or control subjects who are healthy. Claims 94-105 all include statements regarding the indication of schizophrenia or lack thereof based upon the comparison of the

quantified level and the control levels, and claims 106-111 include a step of classifying the test subject as being a candidate for or not being a candidate for having schizophrenia based upon the comparisons.

The nature of the invention requires the knowledge of a reliable association between comparing BTG2 expression and the indication that schizophrenia is present in a human.

Scope of the claims

Here the scope of the claims includes, in many cases, making conclusions based on a fold difference of "at least 2," where the specification does not provide support for such a broad limitation (see rejection for new matter in this office action).

Teachings in the Specification/Examples

Regarding schizophrenia, the specification provides example 27 wherein gene expression profiles of blood samples from individuals having schizophrenia were compared with normal individuals, that is healthy patients. The specification teaches that 1,952 genes were identified as being differentially expressed, and regarding the instant claims, table 3Y provides a list of these genes (Example 27). BTG2 is among the genes.

Table 3Y teaches that the ratio of expression in schizophrenic samples relative to control samples is 2.46, indicating that in the tested samples, BTG2 was expressed, on average at a 2.46 times higher level in schizophrenic patients versus healthy controls. Table 3Y teaches that this result is significant p=0.0076.

The specification further provides example 51 which compares gene expression in patients having schizophrenia versus patients having manic depression syndrome. The specification teaches that 294 genes were identified as being differentially expressed, and

regarding the instant claims, table 3AC provides a list of these genes (Example 51). BTG2 is among the genes. The table teaches that there is a p-value of 0.0013 for BTG2 expression, but the specification does not provide any guidance as to the level of "difference" between expression in the two populations, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples.

State of the Prior Art and Level of Unpredictability

The expression of genes in example 27 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. The specification does not teach replication of the disclosed experiments in an external cohort of individuals.

Indeed, the need to replicate findings based on differential expression analysis is supported by other writers in the prior and post-filing date art. Michiels et al. teach that molecular signatures developed based on differential expression data strongly depend on the selection of patients in the training sets, and advocate the use of validation by repeated random sampling (Michiels et al. Lancet, 2005; 365:488-492). Michiels et al. further teach that studies

with larger sample sizes are needed before gene expression profiling can be used in the clinic. In the example relevant to the instant claims, the sample sizes were quite small- namely 4 patients having schizophrenia versus 6 healthy control individuals (Figure 26).

Slonin teaches that a common problem when developing classification schemes based on differential expression data is 'overfitting' the data (Slonin, Nature Genetics Supplement, Vol. 32, December 2002, pages 502-508) . As a consequence, when using differential expression data to develop classification schemes, classification of the training samples may well be perfect but subsequent attempts to classify new test data fail miserably. Here there has been no attempt to validate the classification scheme based on BTG2, and so it remains highly unpredictable as to whether or not classification based on relative expression of this gene would be successful. Baker also cautions that in the development of classifiers a major problem is 'overfitting' meaning that if one investigates enough classification rules, then by chance one of them is likely to perform well, and that data from samples used to develop classifiers should be split to create samples for validations (p.512, right col., lns.1-8), and that larger sample sizes should be used (p.513, left col., lns.17-31) (Baker. Journal of the National Cancer Institute, Vol. 95, No. 7, April 2, 2003).

Iwamoto et al. teach that expression profiling in psychiatric fields have been notoriously discordant, with different studies often reporting conflicting gene expression data (The Neuroscientist, Vol. 12, Number 4, 2006, pages 349-361; Abstract and page 351). Tsuang et al. undertake an analysis that is very similar to the one in the instant specification. Regarding their results, Tsuang et al. caution that the results must be interpreted with caution given several limitations including small sample size, the fact that the findings are not replicated in a separate

cohort and results "may represent chance findings and type-I inferential errors," and that the patients tested were all on drugs that were not accounted for in the analysis (American Journal of Medical Genetics, Part B (Neuropsychiatric Genetics) 133B:1-5(2005)). All of these cautions set forth by Tsuang et al. appear to be equally relevant to the study set forth in the instant application. Vawter et al. teach that there is lack of consistency in the study of genes differentially expressed in schizophrenia which might be related to etiological and genetic heterogeneity of the illness (p. 42, Vawter et al. Schizophrenia Research, Vol. 67, pages 41-52, 2004). Further, Vawter et al. teach that genes that are significant by a t-test may not exceed the threshold for fold of change to be considered above background expression (p. 46). All of these taken together underscore and highlight the very unpredictable nature of this technology area.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression

is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention due to the lack of validation and replication of the observed differential expression of BTG2. In order to practice the claimed invention, one would have to replicate the experiments set forth in the specification on different populations of individuals in order to determine that any relative observation of a difference greater than 2 or 2.5 or even 2.49 is sufficient to conclude that schizophrenia is indicated. The issue here is that success is not guaranteed, and indeed the results remain highly unpredictable, as discussed by the references cited in the previous section. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

Conclusion

The claims include methods which encompass the detection in blood of the expression of BTG2 in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of schizophrenia," or some similar language. The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks

Applicant traverses the enablement rejection with discussion beginning on page 13 of the response. Any argument or statement not particularly addressed is not contested. For example on the top of page 14 applicant points out that in the pending claims control subjects are limited to healthy controls and individuals having schizophrenia. Other such undisputed statements are not particularly addressed.

Applicant argues that one skilled in the art can make and use the claimed invention without applicant disclosing the direction or level of the difference that exists between patients having schizophrenia and those who do not have schizophrenia. This argument is not relevant to the instant claims which all recite a direction of difference and some minimal level of relative difference.

Applicant states that the teachings of Tsuang et al. clearly support the experimental data disclosed herein as being reliable, and corroborate Applicant's disclosure. Insofar as applicant is trying to rely on the post-filing date reference to support the enablement of the claimed invention, applicant is reminded that the invention must be enabled as the time of filing, and that non-patent literature cannot replace evidence on the record. Applicants point to Tsuang et al. where they suggest that the work demonstrates the **potential** utility of blood-based RNA profiling in diagnostics (emphasis mine). Applicant states that their use of "potential" refers to the infancy of commercial diagnostics for schizophrenia, and does not refer to the reliability or predictability of such diagnostic methods. However, this analysis is not supported by the reference. Tsuang et al. specifically teach that to validate their results and overcome the limitations of sample size and inferential errors, their "approach must be extended to larger

extensively characterized sample sets, and the convergence of several lines of evidence will ultimately determine the reliability and usefulness of the identified putative biomarker genes…" and that "future investigations will be performed on drug-naïve patients or their non-psychotic first-degree relatives (p. 4)." Applicants state that the cautionary statements in Tsuang et al. represent a maximally conservative standard such as the one used by the FDA. However, this is not supported by the references of record which are also cited in the enablement rejection, all of which emphasize the importance, and indeed necessity of validating classification schemes based on expression data due the unpredictable nature of this technology. Furthermore, the examiner has made all of her rejections under the laws which determine patentability, and is not using the standards for use by the FDA. Applicant's suggestion as much is misplaced. Tsuang et al. cannot be mistaken as suggesting that even the work they did was sufficient to establish the use of a single differentially expressed gene as sufficient to indicate the presence of schizophrenia or to classify individuals.

The aspects of the rejection which discuss BTG2 being expressed in other diseases have been withdrawn in view of the newly added claims.

The rejection is modified to address the newly added claims, and maintained.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

January 14, 2009